What’s In a Name?

The value of knowing the cause of developmental delay

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Objectives

a) Review of what happens in a genetic counselling appointment, what information is gathered, and potential outcomes

b) Review of new technologies

c) Understand the challenges and benefits of determining the etiology of intellectual disability

Participants will learn when to refer, what to expect during a counselling appointment and what the potential benefits of a genetic assessment are for an adult with developmental disability and for their family.
The Role of Genetics in Medicine

What to Expect During a Genetics Consultation

New Technologies used to Diagnose a Patient

When & How to Refer a Patient

Syndrome discussion
Genetics in Medicine
What to Expect During the Genetics Process
Our team is made up of Geneticists, Genetic Counsellors and support staff.

**Geneticists** are medical doctors who specialize in Genetics. Geneticists review the family and medical history and examine patients who have been referred, to diagnose genetic conditions.

**Genetic counsellors** typically have a postgraduate university degree, a Masters of Science, specializing in medical genetics. Genetic counsellors are able to interpret complex genetic and medical information and explain it in terms understandable by most people. They are trained in assessing family histories, providing information about genetic conditions and how genetic conditions occur in families.
Prior To The Genetics Appointment

• Information gathering
  – Results of previous investigations
  – Imaging studies
  – Specialists’ consult notes

• YOU can encourage patients/family members to gather relevant information from other family members
  – Others in the family with similar features
  – Photographs
  – Prenatal history
Genetics Appointment

- Discuss reason for referral and establish goals and expectations for consultation

- Family History
  - Inheritance pattern
  - Ethnicity
  - Consanguinity
  - Seemingly unrelated symptoms
    - VCF – cleft lip/palate; mental health issues; heart defect; learning disability
Genetics Appointment (cont’d)

• Review of Medical History
  – Prenatal
  – Postnatal
  – Hospitalizations/surgeries
  – medications
  – Other consultations with specialists
  – Current health

• Physical Exam
  – Height, weight, HC
  – Skin findings
  – Measurements & body proportions
  – Exam for unique and/or subtle features
• Differential Diagnoses
  – Based on review of family history, medical history and physical exam

• Discussion of Relevant Investigations
  – biochemical testing
  – “general” genetic testing (microarray)
  – testing for a panel of related conditions
  – testing for a single disorder
  – recommend/arrange specialists’ consultation
Advances in Genetic Testing:

G-BANDING VS MICROARRAY
G-band Analysis

“Big” picture

Ability to detect:
- deletions/duplications >5 to 10Mb
- aneuploidy
- translocations
- inversions

• Interpretation of abnormality: usually clinically significant
Regions of gain or loss can be found anywhere in the genome.
Sample Preparation
Array CGH: The Complete Process

Steps 1-3 Patient and control DNA are labeled with fluorescent dyes and applied to the microarray.

Step 4 Patient and control DNA compete to attach, or hybridize, to the microarray.

Step 5 The microarray scanner measures fluorescent signal intensity.

Step 6 Computer software gathers the data and generates a plot.
Microarray Result

control

Subtelomeric deletion
G-banding + FISH

- Retrospective Study:
  - N = 36,325 patients with DD/MR
- Detection Rate by:
  - G-banding: ~4.5% abnormal unbalanced karyotype
  - Targeted FISH: ~3.5% abnormality detected

Microarray

- ~12% diagnostic yield
  - 29 studies from PubMed
  - Patients with DD/MR AND normal karyotype

If microarray had been used as a first tier test
Detection rate would have been ~20%
WHAT IS “NORMAL?”

Interpreting Microarray Results:
Phenotype Identified Genotype

COMPOSITE OF CHROMOSOME 22
46,XY.del(22)(q11.21q11.23)
Genotype Defining Phenotype

Deletion 2q23
Minimum overlap of 250 kb
Includes MBD5 gene

Clinical Symptoms (>50% of patients):

- Developmental delay, language impairment
- Stereotypical repetitive movements
- Seizures
- Ataxia
- Growth retardation
- Microcephaly
- Minor hand and foot anomalies
Determining Pathogenicity of Abnormality

- research existing databases (DECIPHER, ISCA)
- review of published case studies
- protein modelling & conservation throughout evolution
- family studies
Search Existing Databases & Consortia
Follow up

• Result(s) of investigations do not provide a diagnosis
  – Further testing
  – Follow up in “X” years

• Further studies recommended to interpret result

• A diagnosis is made!
Diagnosis Is Made!

• Implications for patient
  – Explanation for differences can be provided
  – Prognosis
  – Establishing a management plan
  – Recurrence risks/prenatal testing

• Implications for family members
  – Recurrence risks
  – Prenatal testing
Patient RS

- Seen at 9 years old in Genetics with developmental concerns
- Referred by neurologist
- Prenatal
  - Unremarkable
- Birth
  - NSVD
  - Wt: 7lbs
- Family history
  - East Indian descent
  - 2 older sisters
  - Otherwise unremarkable
Patient RS

- **Developmental Hx**
  - Gross motor skills – nl
  - Delay in fine motor skills
  - Difficulties focusing attention
  - Behavioural concerns
  - Speech delay

- **Physical Exam**
  - Not strikingly dysmorphic
  - No eye contact; no play

- **Previous Investigations**
  - Chromosomes & fragile X – nl
  - MRI: “non-specific periventricular linear and more confluent lesions in the white matter peritrigonal area and corona radiata”
Microarray Result
ELN Duplication

Q-PCR RESULT
de novo

<table>
<thead>
<tr>
<th>Individual</th>
<th>Chr / Gene</th>
<th>Quantification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proband</td>
<td>7q11.23/ CLIP2</td>
<td>3 copies</td>
</tr>
<tr>
<td>Father</td>
<td>7q11.23/ CLIP2</td>
<td>2 copies</td>
</tr>
<tr>
<td>Mother</td>
<td>7q11.23/ CLIP2</td>
<td>2 copies</td>
</tr>
</tbody>
</table>

arr 7q11.23(72,046,538-73,831,310)x3
Implications for RS & Family

• *De novo* – low recurrence risk; 50% for RS
• Limited case studies
  – Variable cognitive deficits
  – Behaviour difficulties
  – Subtle facial appearance: short philtrum, flat eyebrows, tall forehead
  – Risk for mental health issues
Etiology

- Developmental Disability
  - 40% unknown
  - 20% acquired
  - 40% genetic
average of 5.4 problems per patient
almost 2 of 3 individuals reported no symptoms
24 % of caregivers said there were no problems
Corollary: knowing the etiology for ID may give you “advance warning” of the types of medical problems to expect – and perhaps management strategies
• Family story

• Treatment ....
When is a referral to genetics appropriate?

- Intellectual disability of unknown etiology
  - Mod-Severe ID
  - Dysmorphic features
  - Congenital malformations
  - Specific physical and/or behavioural phenotype
  - Positive family history
Themes

Pattern Recognition
  Physical Appearance
  Behavioural

Complexity
  Genomic
  Behavioural

Management Strategies/Treatment…..
Genes contain instructions for making proteins.

Proteins act alone or in complexes to perform many cellular functions.
Some “Genetic Errors” that can cause Syndromes in which there is ID

- Whole chromosome
- Contiguous gene segment
- Single gene
- Imprinting
Physical Pattern Recognition
Hehr, U et al. Wide phenotypic variability in families with holoprosencephaly and a sonic hedgehog mutation
At least 7 genes can cause Holoprocencephaly

- **SHH**
  - Chromosome 7
  - 30-40% AD
- **HPE5**
  - Chromosome 13
  - 5% AD
Minor Anomalies

- Some minor anomalies are external markers of specific occult major anomalies.
- Many malformation syndromes are recognizable as patterns of minor anomalies.
- 15% of normal newborns have one or more minor anomalies. Three or more minor anomalies is distinctly unusual.
Behavioural Pattern Recognition
Can you match behavioural phenotypes and genotypes?

• Characteristic but not exclusive
• Exceptions always occur
• May not be one gene - one phenotype
• The “genetic milieu” is an important modifier (e.g., in Fragile X)
• Environment
• there may be overlap between syndromes
• knowledge of characteristic patterns may be helpful for diagnosis, prevention and management
“Genetically driven”

- Hyperphagia in Prader Willi Syndrome
- Anxiety in Fragile X
- Hand-wringing in Rett syndrome
- “nail yanking” in SMS
Some Syndromes with Identifiable Behavioural Phenotypes

• Fragile X Syndrome
• Smith-Magenis syndrome
• William syndrome
• Velocardiofacial Syndrome
• Prader-Willi syndrome
• Angelman syndrome
Gene Reviews at:

Fragile X Syndrome

- The commonest heritable form of developmental disability is the Fragile X Syndrome
- Frequency $\geq 1/4000$ boys, $1/8000$ girls
- trinucleotide repeat expansion
FMR1 – the Fragile X gene

- A CGG trinucleotide repeat is found at one end of the FMR1 gene
- In most people the repeat size is 6 to ~ 50
- Expansion of the repeat segment produces premutations and mutations
Repeat Size

- 6-45 normal
- 45-60 grey
- 60-200 premutation
- >200 full mutation
2 year old male

- Moderate ID
- Autistic features
  - Avoids eye contact
  - Repetitive actions
- Callous on the back of his hand from biting
- Hyperactive
Family History

• Mother
  – Thought to have premature ovarian failure
  – Family history unremarkable
Family History

- Grandfather:
  - Retired high school principal
  - Has noticed a tremor x 3 years
  - Now has some difficulty with balance and memory
ACMG Guidelines for Diagnostic and Carrier Testing

- Genetics in Medicine, 7(8):584-587, 2005
Test for the Fragile X syndrome in Individuals:

- With ID or autism, “especially if they have”
  - Features suggestive of FRAX (physical or behavioural)
  - Family history of ID NYD
  - Family history of FRAX
Full mutation - Males

- Almost all have intellectual disability and similar physical and behavioural features
- Physical features: Long face, large ears, macro-orchidism, hyperextensible MCP joints, hand calluses
- Behavioural features: Avoidance of eye contact, hyperactivity, hand flapping, perseveration
- PWS subtype
Full Mutation - Females

- Females – 1/3 normal intelligence, 1/3 borderline intelligence, 1/3 intellectual disability
- Usually less typical facial features
Clinical Concerns

• Epilepsy:
  – Tonic-clonic
  – Complex partial

• Visual problems:
  – Strabismus
  – Refraction errors
Clinical Concerns

• Ear infections, hearing loss
• Obstructive sleep apnea
• Mitral valve prolapse (adults), aortic root dilatation
• Joint hyper extensibility, congenital hip dislocation, pes cavus, scoliosis
Clinical Concerns

- UTIs
- Inguinal Hernias (15%)
- Endocrine:
  - Precocious puberty (females)
  - PMS
Behavioural Features

- Problems with sensory integration, tactile defensiveness – tantrums
- Hyperactivity
- Hand flapping/biting
- Poor eye contact
- Social anxiety – aggression
- OCD – person/activity
- Autism – up to 30%
Management

• Sensory hyperdefensiveness
  – “Sensory diet” (OT)
• Anxiety and hyperarousal
  – SSRIs
• Attention problems
  – Ritalin
• Aggression
  – SSRIs, Risperdone
Interventions

• Avoid sensory overload – weighted vest
• ADHD management:
  • Seat close to the teacher, short tasks, reward
  • Maintain calm environment
• Plan transitions
• Picture board
• Maximize strengths – sense of humour, social relationships, visual skills, long term memory
• Educational materials for teachers and EAs
Resources

- www.fragilex.org (National Fragile X Foundation)
Figure 1 | Speculative model for FMRP shuttling between the nucleus and cytoplasm. Fragile X mental retardation

Therapeutic Implications?

- evidence suggests one consequence of the loss of FMRP in neuronal dendrites is exaggerated signaling via Gp1 mGluRs (group 1 metabotropic glutamate receptors)
Figure 1 | Speculative model for FMRP shuttling between the nucleus and cytoplasm. Fragile X mental retardation

Clinical trials are assessing drug therapies that specifically target signaling by Gp1 mGluRs

- Evidence that mGlu5 antagonists are effective anxiolytics
Fragile X Summary

- Males and females affected
- Specific physical and behavioural patterns
- Notable clinical concerns
- Specific medical management of behavioural concerns
- Specific educational interventions
- New, targeted therapies
Smith Magenis Syndrome (del 17p11.2)
Clinical Characteristics

- Congenital abnormalities
  - heart, palate, hearing, urinary tract
- Vision, hearing (ear infections)
- Sleep disturbance – circadian rhythm
- HNPP, peripheral neuropathy
- Scoliosis
- Elevated cholesterol in childhood
Developmental Characteristics

- Speech delay, Hoarse voice
  - Palatal abnormalities
  - Sign language
- Visual learning preference
  - Facility with computers, puzzles (Rubik’s cube)
“Specific” Behavioural Characteristics
- onychotillomania
- polyembokoilomania
- self-abuse
- obsessive compulsive tendencies
- hugging (self and others)
Positive behaviour

• Loving
• Empathic
• Sense of humour
• Appreciative
• Affectionate
Behavioural concerns

• Attention seeking
• Self-injury
• Attention deficit
• Explosive behaviour
• Prolonged tantrums
• Destructive, aggressive
Behavioural Strategies

- Information is from the UK and USA SMS support group websites (www.prisms.org)
- Consultations are available with Brenda Finucane and Barbara Haas-Givler at Genetics at Elwyn, Elwyn, Inc
Triggers

- Physical concerns can cause behavioural concerns – change in behaviour may signal a medical problem – eg ear infection, tooth ache
- Environmental changes
- Death in the family
- Exacerbated in SMS by:
  - Delayed speech – speech therapy and sign language
  - High pain threshold
  - Sleep problems
  - Incongruent level of maturity?
Developmental Asynchrony

• “Embrace the inner toddler” – 10 year old body, 5 year old cognition, 2 year old behaviour
• Anxiety, frustration, can’t communicate
• No cure
• First change your approach
• Modify the environment?
• Choose what needs to be modified
• Give them some control
Treatment of Sleep Disturbance

• Modification of the bedroom
  – Black-out curtains
  – Removal of toys, small objects
  – Locks and alarms

• Melatonin and acebutalol

• Light therapy???
VCFS/22q Deletion Syndrome

- VCFS (Cleft palate, velopharyngeal insufficiency, speech, learning difficulties)
- DiGeorge (CHD, hypocalcemia, immunodef)
- microdeletion of 22q11 first identified 1991
VCFS/22q deletion syndrome

- 1/2000 - 1/4000
- Microdeletion – 24-45 genes, no clear critical region or one gene
- 10% family history
- TBX1 – CHD
- 9 genes (including COMT) implicated in neuropsychiatric concerns
Multisystem Disorder

- characteristic facies,
- VPI,
- immune deficiency (thymic hypoplasia),
- congenital heart disease,
- hypocalcemia,
- low platelet count,
- intellectual disability (borderline –mild with some specific strengths and weaknesses)
- Neuropsychiatric concerns, including anxiety, depression, schizophrenia (60% of adults)
Impact of diagnosis on an adult male

- Mother learnt of etiology of psychosis and obtained some closure
- Family members tested
- On-going management through research program
  - Calcium levels
  - Cardiac assessment
  - VPI
  - Immune status
MECP2 Turned On

MECP2 Turned Off

Increasing symptoms of inertia, abnormal gait, hindlimb clasping, tremor, irregular breathing and poor general condition

Returned to close to a normal phenotype
What if the cause is not known?

• Keep looking!
  – New understanding of genetic mechanisms
  – New technologies
  – Newly described syndromes with recognition of behavioural phenotypes as part of the syndrome
  – May take years
Case 1

- 35 year old female
- Moderate degree of intellectual disability of unknown cause
- 5’2”, 160 lbs
- Sleeps poorly
- Recently:
  - Temper tantrums escalating
  - Self abuse and aggression
Case 1

• What would you do to assist your client?
• How might your approach change if you knew she had Smith Magenis syndrome?
Sue

- 6 year old female
- 110 cm, 35 kg
- Poor sleep
- Hoards, OCD
- Almond shaped eyes, small hands and feet, obese
- As an infant, floppy, poor weight gain
Sue

- Prader Willi Syndrome
- Sleep study for obstructive sleep apnea
- Behaviour management for hyperphagia
- Meds – Growth Hormone, Topiramate?
- Heimlich maneuver
- Vomiting may signal emergency!!
Lindsay

- Limited speech – 2 words
- Seizures
- “wobbly gait”
- Flaps her hands
- Laughs “inappropriately”
• Non-verbal communication – picture boards, signing – receptive language > than expressive
• Sleep often disrupted
• Don’t mistake body movements for seizures (may lead to overmedication)
Thank You